

A mini review on biological potential of 1,3,4-oxadiazole derivatives

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Abstract

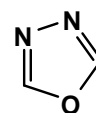
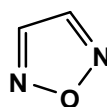
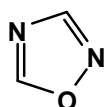
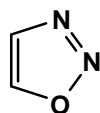
Among heterocyclic compounds, 1,3,4-oxadiazole has become an important synthons in development of new drugs. Compounds containing 1,3,4-oxadiazole cores have a broad biological activity spectrum, including antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antidepressant, anticonvulsant, and anti-diabetic properties. The ability of 1,3,4-oxadiazole heterocyclic compounds to undergo various chemical reactions has made them important because of their privileged structure, which has an enormous biological potential.

Keywords: Heterocyclic compound, 1,3,4-oxadiazoles, Biological activities.

Introduction

1,3,4-Oxadiazole is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five-membered ring. Oxadiazole rings contain two carbon atoms, two nitrogen atoms, and one oxygen atom. Although 1,3,4-oxadiazoles have been known for about 80 years, it is only in the last decade that investigations in this field have

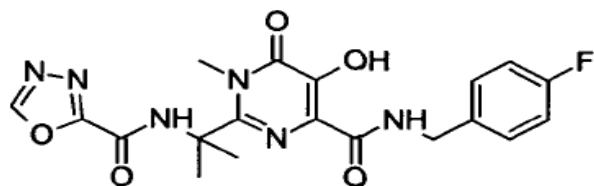
been intensified. It is derived from furan by substitution of two methylene groups with two nitrogen atoms. There are four isomers of oxadiazoles: 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,2,3-oxadiazole and 1,2,5-oxadiazole. However, 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known, and more widely studied by researchers because of their many important chemical and biological properties.¹⁻⁵



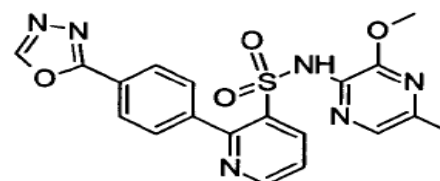
1,2,3-oxadiazoles 1,2,4-oxadiazoles 1,2,5-oxadiazoles 1,3,4-oxadiazoles

This is primarily due to the number of uses of 1,3,4-oxadiazoles in the most diverse areas, for example in drug synthesis, scintillating materials, and the dyestuffs industry. Research is also in progress to explore the various biological activities of 1,3,4-oxadiazoles. Some of the activities are mentioned here. The compounds containing 1,3,4-oxadiazole unit currently used in clinical medicine are: Raltegravir, an antiretroviral drug and Zibotentan, an

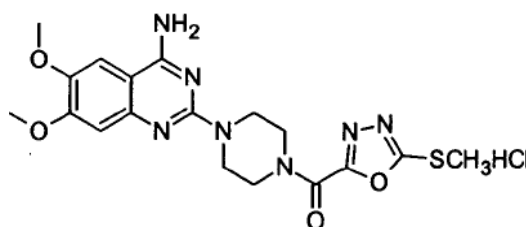
anticancer agent. Oxadiazole nucleus is present in antihypertensive drugs such as Zibotentan, nesapidil and antibiotics such as furamizole.⁶⁻⁸ GABA-modulating 1,2,4-oxadiazole derivatives are known for their anticonvulsant activity. 2,5-Disubstituted 1,3,4-oxadiazoles have also attracted great interest due to their applications in organic light emitting diodes, photoluminescence, polymers and material science.



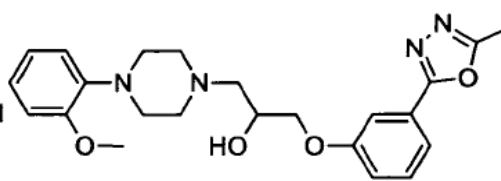
Raltegravir



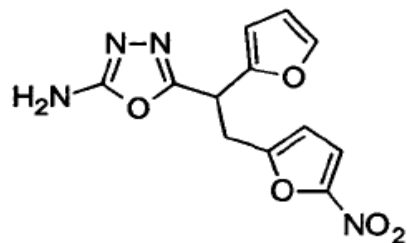
Zibotentan



Zibotentan

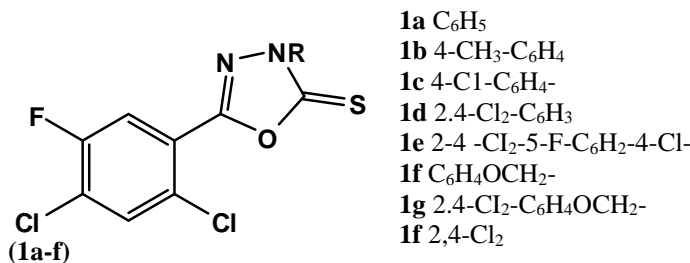


Nesapidil

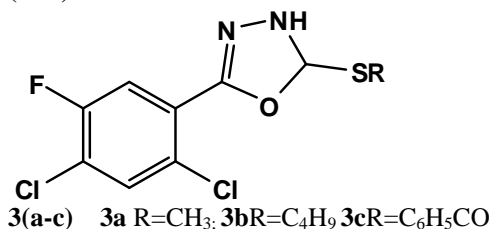


Furamizole

Anticancer and Antimicrobial activity: Some new fluorine containing 1,3,4-oxadiazoles (**1a-f**), (**2a-c**) and (**3a-c**) as potential antibacterial and anticancer agents. Most of

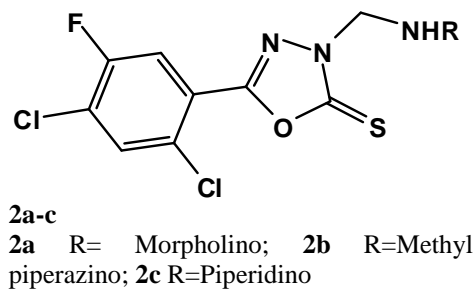


- 1a** C₆H₅
- 1b** 4-CH₃-C₆H₄
- 1c** 4-Cl-C₆H₄
- 1d** 2,4-Cl₂-C₆H₃
- 1e** 2,4-Cl₂-5-F-C₆H₂-4-Cl
- 1f** C₆H₄OCH₂-
- 1g** 2,4-Cl₂-C₆H₄OCH₂-
- 1f** 2,4-Cl₂

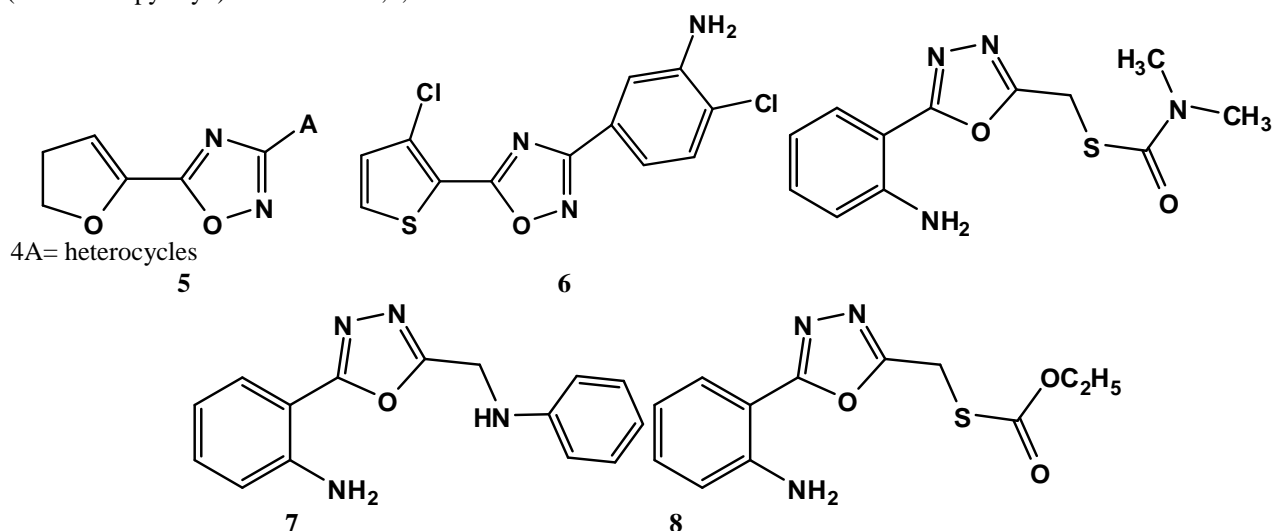


The 3,5-disubstituted-[1,2,4]oxadiazoles (4 and 5) and analogs as activators of caspases and inducers of apoptosis.¹⁰ *In vitro* anti-proliferative activity of some novel 5-(2-amino-3-pyridyl)-2-thioxo-3/f-1,3,4-oxadiazole

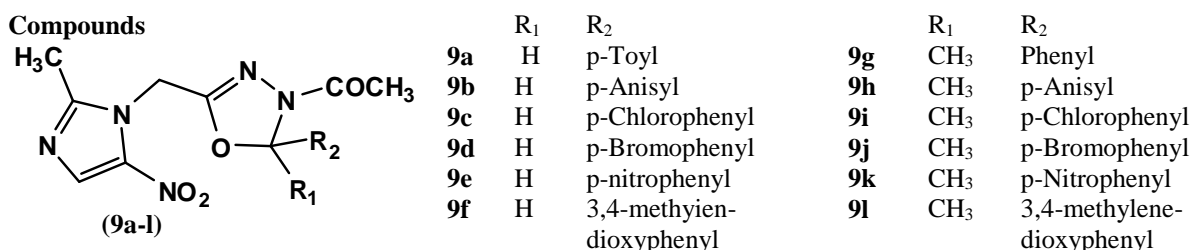
them showed promising antibacterial activity. Also two out of nine compounds showed anticancer activity in the primary anticancer assay.⁹



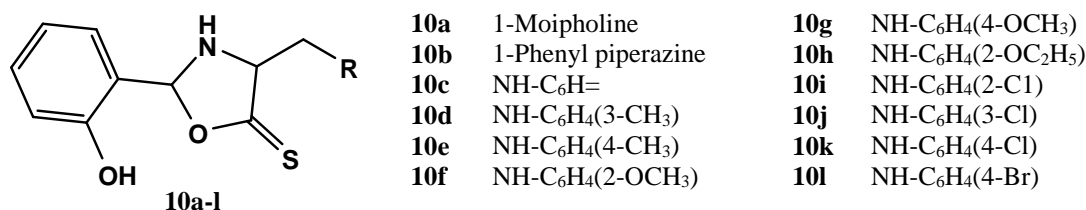
derivatives 6-8. One of the oxadiazoles showed cytotoxic activity against the cells of 4 human cell lines.¹¹



Antimicrobial activity of 1,3,4-oxadiazoles carrying imidazole moiety (9a-l). Most of the tested compounds showed promising antibacterial and antifungal activity.¹²

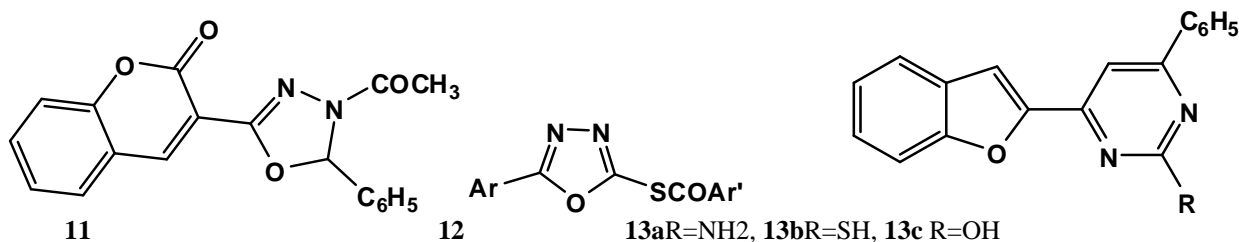


Anticancer activity of novel 5-(2-hydroxy phenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives (10a-l). Some of the compounds produced a good anticancer activity [12a].



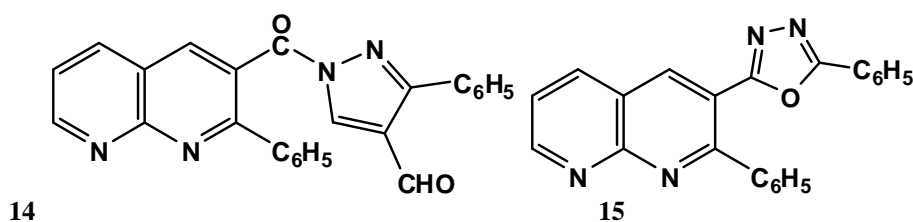
Antibacterial activity of coumarin incorporated 1,3,4-oxadiazoles 11. Most of the compounds showed moderate antibacterial activity¹³ and evaluated the antibacterial activity of 5-aryl-2-arylthio-1,3,4-oxadiazoles 12.¹⁴ The antifungal activity of new 1,3,4-oxadiazolo [3,2-b]-s-triazine-5-ones

and their thione analogues 13a-c. Antifungal activities of the prepared compounds have been compared with Dithane M-45 against *Phytophthora infestans* and *Collectotricum falcatium* and the results correlated with their structural features.¹⁵



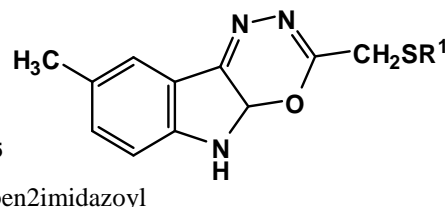
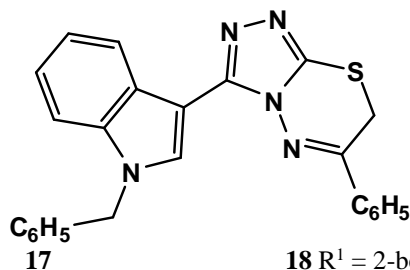
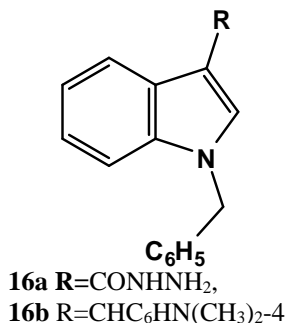
Antibacterial activity of pyrazole and 1,3,4-oxadiazole derivatives of 2-phenyl-1,8-naphthyridine compounds 14 and

15 have been tested for their antibacterial activity using streptomycin as a reference compound.¹⁶



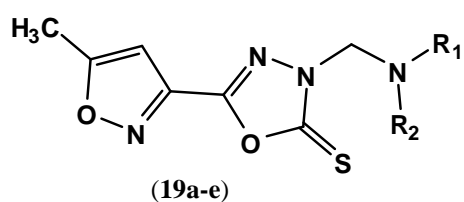
Antimicrobial activity of some new indoiyl 1,3,4-oxadiazole, triazole and pyrazole derivatives (16a-b) and 17.¹⁷ The antibacterial activities of some 1,3,4-oxadiazole and pyrazoline derivatives containing 1,3-Naphthyridine moiety.¹⁸ The antihistaminic, antimuscarinic and

antimicrobial activity of some new 2-substituted-[1,3,4]-oxadiazino [5,6'b] indole 18. The compounds has shown H₁-antihistaminic and higher antibacterial activity than the respective standards pheniramine maleate and ampicillin.¹⁹

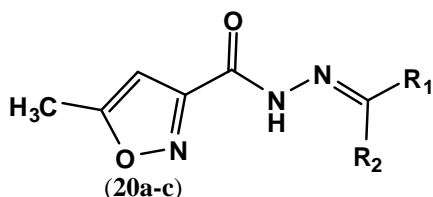


Some oxadiazoles bearing 2-arylamino-5-mercapto-1,3,4-thiadiazole nuclei as possible antimicrobial agents.²⁰

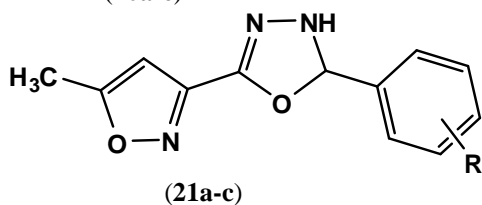
Antibacterial activities of 1,3,4-oxadiazole derivatives containing 5-methyl isoxazole moiety (19a-e)-(22a-c).²¹



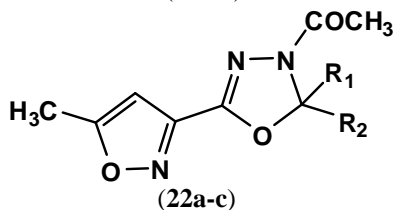
Compounds	R ₁	R ₂
19a	Morpholinyl	Morpholinyl
19b	H	C ₆ H ₅
19c	H	4-ClC ₆ H ₄
19d	H	4-BrC ₆ H ₅
19e	H	4-O ₂ NC ₆ H ₄



20a	CH ₃	C ₆ H ₅
20b	H	4-Cl C ₆ H ₄
20c	H	C ₆ H ₅



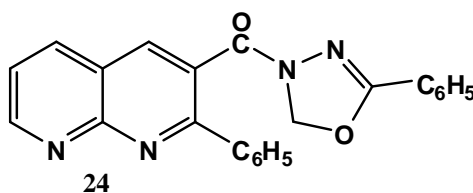
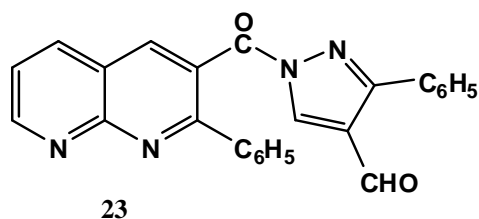
21a	4-H
21b	4-Cl
21c	4-Br



22a	CH ₃	C ₆ H ₅
22b	H	4-Cl C ₆ H ₄
22c	H	C ₆ H ₅

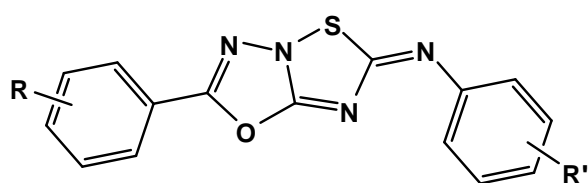
Antibacterial activity of pyrazole and 1,3,4-oxadiazole derivatives of 2-phenyl-1,8-naphthyridine compounds 23 and

24 have been tested for their antibacterial activity using streptomycin as a reference compound.²²



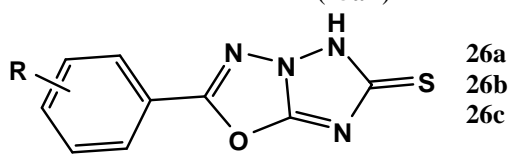
Evaluated the fungi toxicity of fluorinated-1,2,4-triazolo and thiadiazolo [3,2-b]-1,3,4-oxadiazoles (25-i) and (26a-c). The compounds have been tested *in vitro* for their fungicidal activity against *Cephalosporium tacharri*, *Aspergillus niger* and *Fusarium oxysporum* and the results are compared

with their parent thioureas. The structural features of the tested compounds have been correlated with their fungicidal activity.²³ Antimicrobial study of heterocycle substituted S-triazoles, 1,3,4-thiadiazoles, oxadiazoles 27 and related heterocycles.²⁴

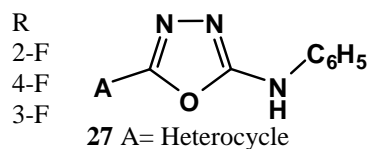


(25a-i)

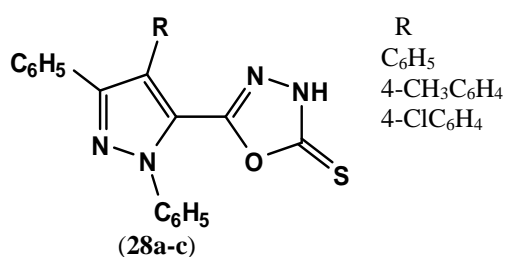
	R ₁	R ₂		R ₁	R ₂
25a	2-F	2-Cl	25f	3-F	4-Cl
25b	4-F	2-Cl	25g	2-F	4-CH ₃
25c	3-F	2-Cl	25h	4-F	4-CH ₃
25d	2-F	4-Cl	25i	3-F	4-CH ₃
25e	4-F	4-Cl			



(26a-c)

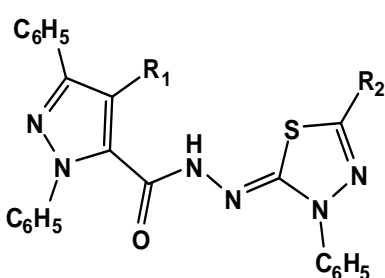


Antimicrobial activity of 5-(pyrazol-5-yl)-1,3,4-oxadiazole-2(3H)-thiones (28a-c) and (29a-c).²⁵



(28a-c)

R
C ₆ H ₅
4-CH ₃ C ₆ H ₄
4-ClC ₆ H ₄

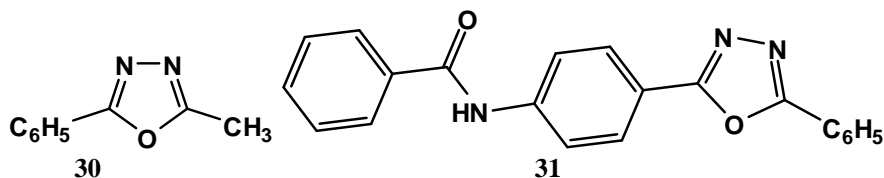


(29a-c)

R ₁	R ₂
C ₆ H ₅	C ₆ H ₅
4-CH ₃ C ₆ H ₄	C ₂ H ₅ O ₂ C
4-ClC ₆ H ₄	CH ₃ CO

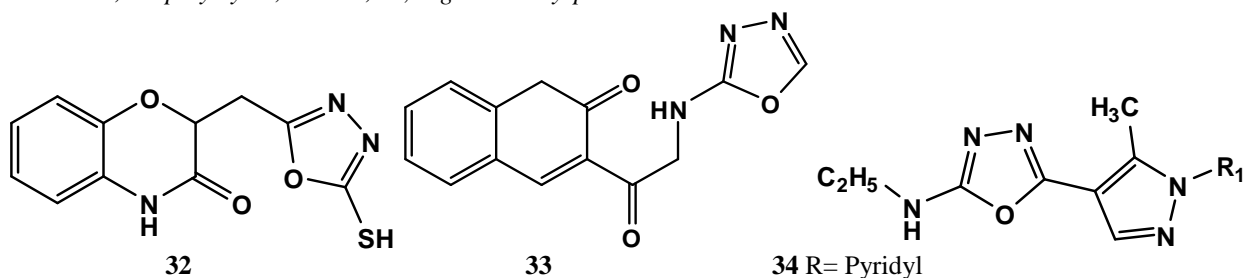
The synthesis and antimicrobial activity of some novel oxadiazole, thiadiazole and triazole derivatives.²⁶ The chloramine-T-mediated synthesis of 1,3,4-oxadiazole along with their antimicrobial activity. Among the compounds tested, few compounds have displayed significant anti fungal activity.²⁷ Various rearrangements and dehydration reactions of 1,3,4-oxadiazoles were worked out extensively.

Polyphosphoric acid influenced dehydration of 1-acetyl-2-aryl-hydrazine and their rearrangements to afford 2-methyl-5-aryl-1,3,4-oxadiazoles 30.²⁸ The synthesis and antimicrobial activity of benzamido phenyl oxadiazole 31, most of the compounds possess bactericidal and fungicidal activity.²⁹



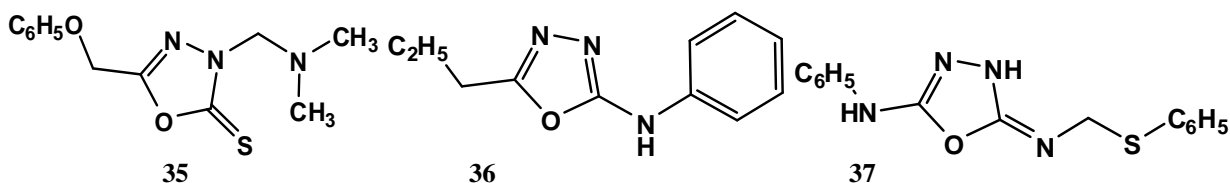
Synthesized and evaluated the antimicrobial activities of oxadiazole, 1, 5-disubstituted-2-mercapto-1, 3, 4-triazole derivatives.³⁰ Synthesized eight 2-(3,4 dihydro-3-oxo-2H-1,4-benzoxazin-2-yl-methyl)-5-alkyl/arylthio)-1,3,4-oxadiazoles 32 from their respective hydrazides. All the compounds were screened for antimicrobial activity against *B. subtilis*, *B. polymyxa*, *E. coli*, *A. niger*, *F. oxysporium*

and *P. griseofulvium*.³¹ Further, condensation of 3-bromoacetyl coumarin and 2-amino-4-phenyl oxadiazole, various oxadiazolyl derivatives 33 showed moderate antimicrobial activity.³² A series of 1,3,4-oxadiazoles 34 by the cyclisation of respective hydrazides. They were screened for their antibacterial, antifungal and antimycobacterial activities.³³



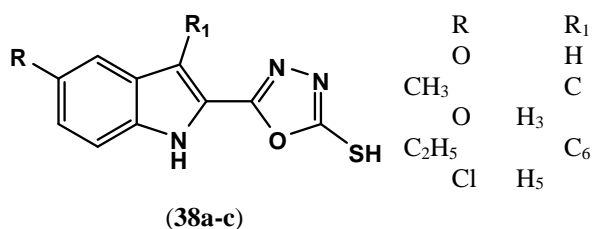
Mannich bases synthesized from 1,3,4-oxadiazoles were screened for biological activities, 3-(2-isopropyl-1,5-dimethyl) phenoxyethyl 4-amino-5-mercapto-1,3,4-oxadiazoles 35 were synthesized starting from thymol. Various amino derivatives were obtained by the reaction of formaldehyde and the oxadiazole-thione.³⁴ The synthesis and antibacterial activity of some novel substituted

oxadiazoles from p-aryl propionyl hydrazines 36, All the compounds showed effective anti bacterial activity.³⁵ A series of 2-(phenylimino)-5-phenyl-thio/phenyl sulfonyl methyl-1,3,4-oxadiazole 37. These derivatives were screened for antibacterial activity against *E. coli*, *K. pneumonia* and *S. aureus*.³⁶



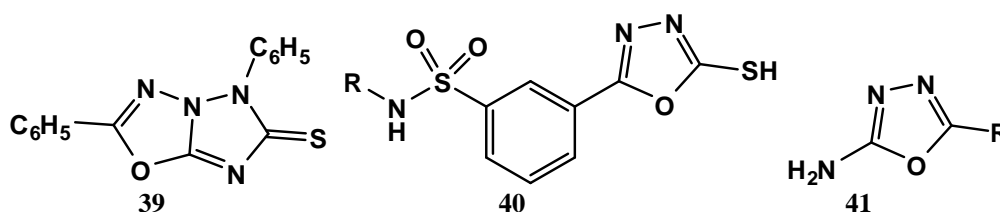
The 2-(5-thioxo-1',3',4-oxadiazol-2'-yl)indoles (38a-c) by the reaction of indole-2-carboxy hydrazides with CS; and KOH. On screening, these compounds showed moderate

activity against *S. aureus*, *E. Coli*, *P. vulgaris* and *B. Subtilis*.³⁷

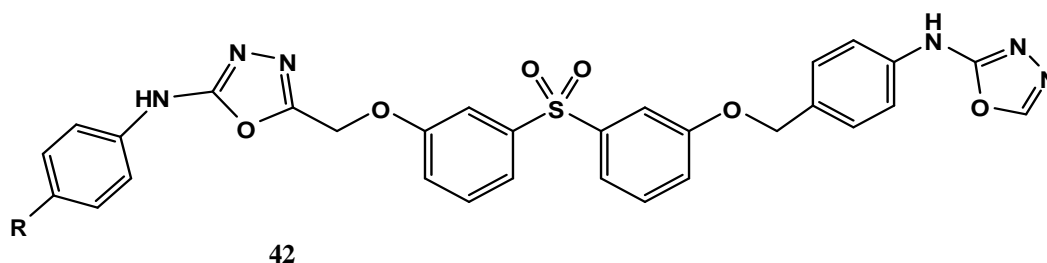


In view of achieving pharmacological compounds of high potency, fusion of 1,3,4-oxadiazoles with various heterocyclic rings by the oxidation cyclisation of the corresponding N-phenyl-N'-(5-aryl-1,3,4 oxadiazol -2-yl) thioureas with pyridine resulting in the synthesis of several 2-aryl]-5-phenyl-1,2,4-triazolo(3,2-b)1,2,4 oxadiazol-6-thione 39. These compounds were screened *in vitro* for fungitoxicity against *A. niger* and *F. oxysporium*.³⁸

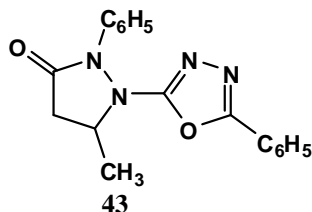
Synthesis of 2-carboxymethyl thio-5-(3 -arylamino sulfonyl)-1,3,4-oxadiazole 40, the reaction of 2-mercapto-1,3,4-oxadiazole with chloroacetic acid gave the product. The product was screened for antibacterial and antifungal activity against *S. aureus*, *E. coli*, *A. niger* and *C albicans*. Moderate activity was obtained.³⁹ Antibacterial and antianioebic activity of substituted amino aryl-1,3,4-oxadiazoles 41. They showed excellent activity.⁴⁰



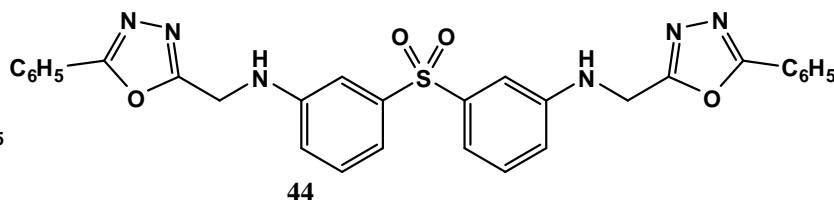
The antibacterial and antifungal activity of p,p'-bis (2-arylamino)-1,3,4-oxadiazol-5'-yl-methoxy diphenyl sulphones 42.⁴¹



The antibacterial activity of substituted 5-aryl-1,3,4-oxadiazoles 43.⁴² The synthesis and antimicrobial activity of

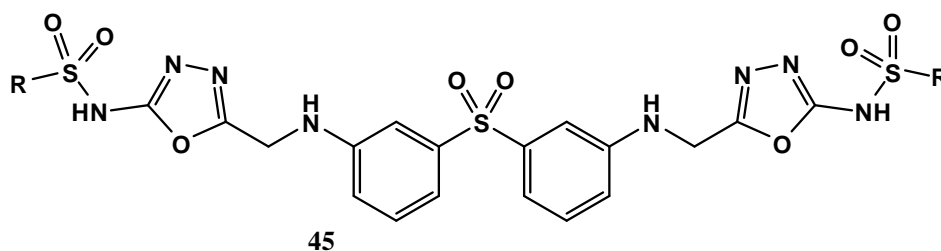


p,p'-bis (5-aryl-1,3,4-oxadiazole-2-yl-methylaraino) diphenyl sulfones 44.⁴³



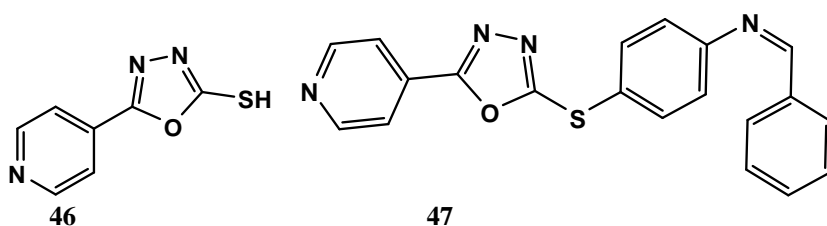
The antimicrobial activity of p,p'-bis[[2-arylsulfonamido)-1,3,4-oxadiazol-5-yl)methyl]amino]

diphenyl sulfones 45. The synthesized compounds were tested for bactericidal and fungicidal activity, most of them showed moderate activity.



The antimicrobial activity of 5-(p-methylbenzoylacetyl)-3-phenyl-1,3,4-oxadiazole. The anti tubercular activity of some new 2-substituted thio 5-(4'-pyridyl)-1,3,4-

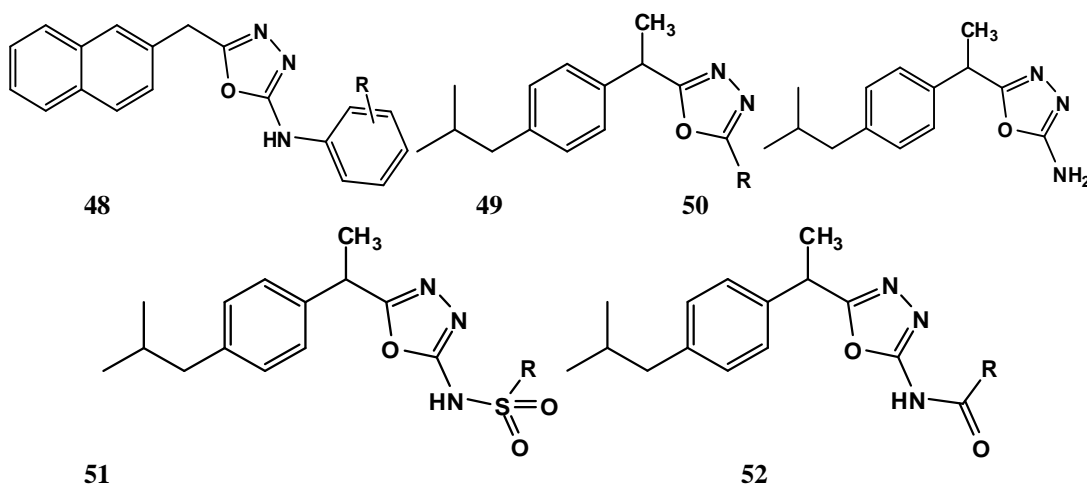
oxadiazoles. Compounds 46 and 47 inhibited the growth of *Mycobacterium* completely at concentration of 20-40 mg/ml of culture medium.



The synthesis and antimicrobial activity of some novel 3,5-disubstituted oxadiazole-2-thiones.

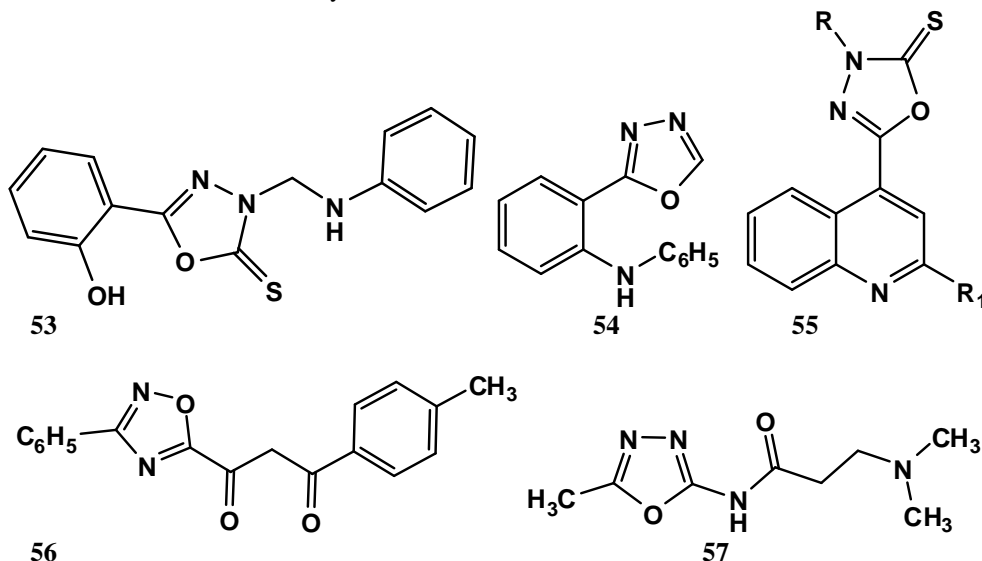
Anti-inflammatory activity: The synthesis and anti-inflammatory activity of Naphthylmethyl oxadiazoles 48. The tested compounds showed 15.58% to 70.13%

inhibition at 100 mg/kg dose compared to ibuprofen which shows 61.04% inhibition at 100 mg/kg dose in carrageenan induced edema in rats. The synthesis and anti-inflammatory activity of substituted 1,3,4-oxadiazole derivatives 49-52.



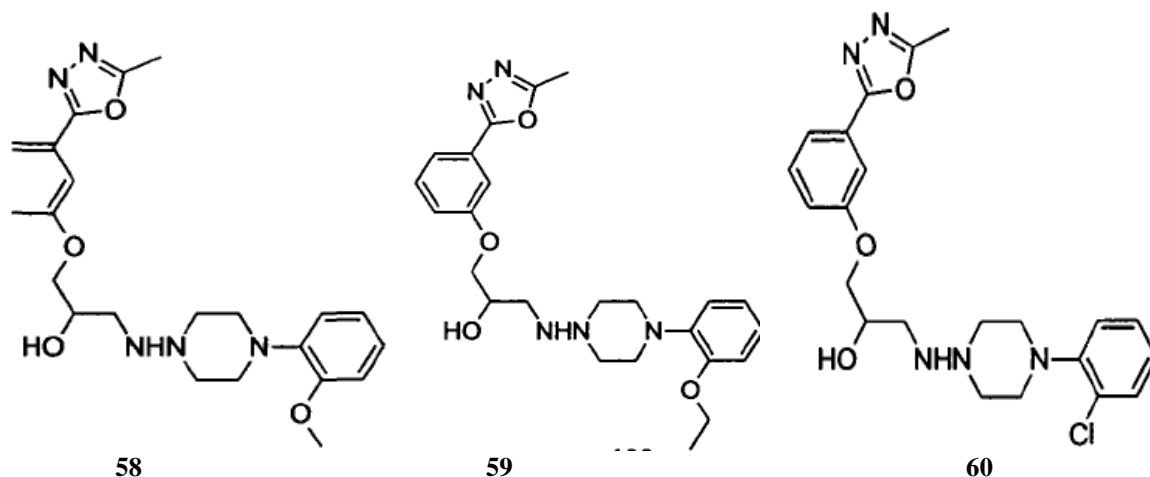
The synthesis and anti-inflammatory activity of some novel 5-(3,5-substituted hydroxyphenyl)-1,3,4-thiazoles, 1,3,4-oxadiazoles and 1,2,4-triazoles. Synthesized 5-(2-hydroxyphenyl)-3-(aryl aminomethyl)-1,3,4-oxadiazole-2-(3H)-thiones 53 and screened for their anti-inflammatory activity by paw edema method in rats. The synthesis of a

series of 5-(2-anilinophenyl)-1,3,4-oxadiazoles 54-56 and their effective anti-inflammatory activity. The spasmolytic and hypotensive activity of 2-(substituted acetyl)amino-5-alkyl-1,3,4-oxadiazoles 57.



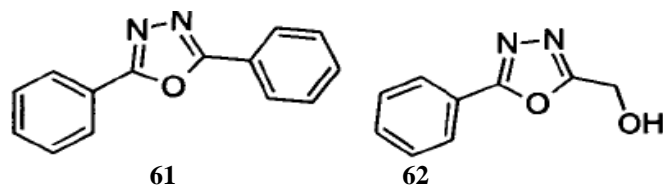
Biologically active molecules containing the oxadiazole moiety include the HIV integrase inhibitor⁴⁴ and the antituberculosis agents.⁴⁵ The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry is evident

from the following examples. 2-Amino-1,3,4-oxadiazoles exhibit muscle relaxants (58-60) and show anti-mitotic activity.



The 2,5-Diaryl-1,3,4-oxadiazoles (61) are platelet aggregation inhibitors. 5-Aryl-2-hydroxymethyl-1,3,4-

oxadiazole (62) display diuretic, analgesic, anti-inflammatory, anticonvulsive, and antiemetic properties.



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